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TITLE: Assessment of Lymphedema Risk Following Lymph Node Dissection and Radiation Therapy for Primary Breast Cancer

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14. ABSTRACT
Lymphedema is a common, chronic, and potentially devastating complication of primary breast cancer therapy. Radiation increases patients' lymphedema risk up to 36% as conventional fields irradiate vital lymphatic tissues. Fusion imaging technologies that combine anatomical and physiological data, e.g. SPECT/CT, may identify lymphatics critical for arm drainage and allow the creation of conformal radiation treatment fields that minimize the exposure of lymph nodes (LNs) and vessels while delivering therapeutic doses to target tissues. This study uses SPECT/CT scanning to localize lymphatics critical for arm drainage, and has established the feasibility of fusing SPECT/CT images with the CT scans used for radiation planning, thereby creating the opportunity to spare essential LNs needless radiation. Further, precise quantification of the dosimetry delivered to LNs draining the arm has revealed harmful levels of incidental irradiation with tangent beam configurations and subtherapeutic exposure with 4-field configurations. Data collection is complete, however interpretation and analysis of follow up SPECT/CT scans is ongoing. Data analysis will address the hypothesis that increased arm volume correlates with high levels of radiation dosimetry delivered to the LNs draining the arm. Additionally, data analysis will determine whether the radiation dose delivered to specific LNs is inversely correlated with radiolabeled tracer uptake, a surrogate measure for functional status, on follow up scans. The proposed study realizes the BCRP goals by elucidating a novel means of refining breast cancer treatment to minimizepatients'riskofdevelopingthemostprevalentanddreadedcomplicationofconventionaltherapy, lymphedema.

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LYMPHEDEMA, RADIATION THERAPY, SURVIVORSHIP, PREVENTION, LYMPHOSCINTIGRAPHY, BREAST CANCER

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Introduction:

The aims of this career development award include: 1) training of the recipient, Dr. Cheville, in the conduct of responsible research and 2) conducting a prospective cohort study to estimate the association between radiation dose delivered to the axillary lymph nodes (LNs) and development of lymphedema (LE), and 3) piloting a novel approach to SPECT/CT-based radiation planning developed during execution of the 2nd aim. Aims 1 and 2 have been completed.

LE is considered the number one survivorship issue by breast cancer patients.[1] LE has recently been identified as a cause of significantly elevated medical expenditures.[2] Its degrading impact on the quality of life of affected breast cancer survivors has been extensively described.[3-6] Breast cancer treatment modifications that minimize damage to the lymphatic system remain the most effective strategy for reducing LE among breast cancer survivors.[7] Thus far such treatment modifications have been restricted to surgical approaches even though radiation damages lymphatics and significantly increases patients' LE risk.[8]

Radiation damage to lymph nodes critical for arm drainage

Body:

Aim 1. Complete course work and a thesis for a Masters of Science degree in clinical epidemiology and the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

Status: Completed

Dr. Cheville, was awarded the degree of Master of Clinical Epidemiology on May 15, 2006. Dr. Cheville's thesis was substantially edited and reduced in length to meet the publication requirements of current cancer journals. The resultant article, "Prevalence and treatment patterns of physical impairments in patients with metastatic breast cancer" has been published.[9] Additional analyses conducted during Dr. Cheville's biostatistical training for her masters' degree have also been published.[10, 11]

Aim 2. Conduct a prospective cohort study to estimate the risk of lymphedema associated with radiation dosimetry to lymph node critical for arm drainage.

Status: Subject enrollment, data collection, and data analysis are complete. An abstract detailing the results of this project have been submitted to the 33rd Annual San Antonio Breast Cancer Symposium, December 8-12, 2010. The status of the abstract is pending.

a. Subject enrollment

Thirty seven subjects enrolled in the study. to undergo repeat scanning.

Data collection

Follow up arm measurements were made in all subjects, however SPECT/CT imaging was obtained from 27 subjects. In all 10 cases of missing follow up SPECT/CT scans, patients refused.

b. SPECT/CT Scan Interpretation

All available pre- and post-radiation SPECT/CT scans have been carefully reviewed by a panel of clinicians and scientists expert in lymphoscintigraphic interpretation.

c. Data Entry

Data entry is complete with regards to variables pertaining to subjects' pre- and post-radiation SPECT/CT scans, demographics, breast cancer, and treatment.

d. Results

Data analysis is complete for subjects' demographic-, cancer treatment- and pre-radiation SPECT/CT scan-related information. These results have been described in our previous annual report dated 8/15/2008.

e. Manuscript Preparation

Proof of concept of the technique developed to estimate individual lymph node dosimetry was detailed in a manuscript published in 2009.[12] The results outlined above regarding incidental and inadequate dosimetry have been submitted as an abstract to the 33rd Annual San Antonio Breast Cancer Symposium, December 8-12, 2010. In addition, 2 manuscripts have been submitted. The first targets a general breast cancer audience and describes the over and under dosing issues outlined in this section. It has been submitted to *Breast Cancer Research and Treatment*. The second describes the association of LE with lymph node irradiation $\geq$ 40 Gy and will target a radiation oncology audience. This manuscript has been submitted to the *International Journal of Radiation Biology and Physics*.

Aim 3. Conduct a pilot study of 30 breast cancer patients requiring tangent beam breast irradiation in order to estimate the reduction in LN dosimetry achieved with SPECT/CT-3 dimension conformal, SPECT/CT-informed intensity modulated, and standard radiation treatment planning. This pilot concept study advances the technique developed in the execution of Aim 2.

Status: Twenty-five patients have been recruited and completed SPECT/CT-based radiation planning. This work has revealed that in a majority of patients undergoing tangent beam irradiation who do not require treatment of their lymph node beds, the dose delivered to lymph nodes critical for arm drainage can be reduced to levels that do not compromise lymphatic function.

a. Subject enrollment

Twenty-five subjects have enrolled in the study. It is unlikely that the target of 30 subjects can be recruited prior to award termination. However, a power calculation based on our preliminary results suggests that a sample of 25 will suffice.

b. Data collection

Data collection has been completed for all 25 enrolled subjects.

c. SPECT/CT-based radiation planning

Radiation planning has been completed for all 25 enrolled subjects. Dosimetry has been estimated for 21 plans, 4 are pending

d. Data Entry

Data entry has been completed for 21 enrolled subjects and is pending dosimetry estimates for the remaining 4 participants

e. Results

Interim data analysis revealed that dosimetry reductions to lymph nodes draining the arm were possible in 100% of subjects. Dosimetry reduction below 40 Gy was possible for 19/21 subjects, 10%

f. Manuscript Preparation

A manuscript draft has been prepared and will be completed once all data have been collected and entered.

Key Research Accomplishments

1. Precise anatomic localization of LNs draining the arm using dual-head Millennium VG gamma camera (GE Healthcare, Waukesha WI) with Hawkeye single-slice CT to generate fusion SPECT/CT images.

2. Manual fusion of GE Hawkeye SPECT/CT scans with CT simulation scans used for radiation planning.

3. Detection of harmful incidental irradiation with tangent beams and subtherapeutic irradiation with 4-field treatment plans.

4. Automated fusion of Phillips Precision generated SPECT/CT scans with CT simulation scans using MIMvista software.

5. Established proof of concept that SPECT/CT-informed radiation treatment planning can reduce harmful incidental irradiation to lymph nodes critical for arm drainage.

Reportable Outcomes

1. Manuscript published describing SPECT/CT-based radiation fusion technique.[12]

2. Platform presentation presented to the National Lymphedema Network meeting in August, 2008.

3. Publication of 3 manuscripts related to work completed during Dr. Cheville's masters' degree training.[9, 10, 13]

Conclusion

Work to date has established that LNs draining the arm after surgical manipulation of the axilla in the context of primary breast cancer can be localized using SPECT/CT scanning. The radiation dose delivered to LNs can be quantified by manually fusing SPECT/CT images with radiation simulation CT scans. Tangent beams deliver potentially harmful radiation doses to 35% of axillary lymph nodes that are critical for arm drainage, while 4-field irradiation fails to adequately encompass all axillary and supraclavicular lymph nodes. LE develops more frequently in women whose arm-draining lymph nodes receive $\geq$ 40 Gy of irradiation. Automated SPECT/CT fusion with simulation CT scans allows the safe reduction of incidental irradiation of axillary lymph nodes.

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